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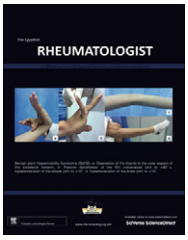

ORIGINAL ARTICLE

The impact of fatigue on health related quality of life in adolescents with benign joint hypermobility syndrome

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Abstract Benign Joint Hypermobility Syndrome (BJHS) is a major source of morbidity in children and adolescents. Due to fatigue and pain, activities of daily living may be limited.

Aim of the work: To investigate the relationship between fatigue and health related quality of life in adolescents with BJHS.

Patients and methods: Thirty adolescents with BJHS and 30 controls were enrolled in the study. All participants were subjected to clinical and laboratory assessment to exclude other causes of fatigue. All were requested to complete self assessment Pediatric Quality of Life (PedsQL) and multidimensional fatigue scale questionnaires. Pain was assessed by Visual Analogue Scale (VAS).

Results: Compared to healthy adolescents, patients with BJHS had a significant lower total score for PedsQL scale (52.56 ± 8.40 and 87.63 ± 4.68 for patients and controls respectively, $p < 0.001$) and a significant lower total score for multidimensional fatigue scale (66.09 ± 13.05 and 91.32 ± 3.97 for patients and controls respectively, $p < 0.001$). General and cognitive fatigue that accompanied BJHS, were the only significant predictors of lower health related quality of life in patients' group. Among patients with BJHS; general fatigue was a significant predictor for emotional and social function impairment, while cognitive fatigue was a significant predictor for school function reduction. Total multidimensional fatigue scale score, general and cognitive fatigue were predictors of physical function impairment in patients and controls. VAS was highly correlated to PedsQL ($r = -0.88$, $p = <0.001$) and multidimensional fatigue ($r = -0.99$, $p = <0.001$) scales.

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Conclusion: This study highlights the importance of fatigue as a significant predictor of poor health related quality of life in adolescents with BJHS.

1. Introduction

Benign Joint Hypermobility Syndrome (BJHS) is an under diagnosed heritable connective tissue disorder, characterized by generalized joint hypermobility and a wide range of visceral, pelvic, neurologic, and cognitive dysfunctions. The syndrome is associated with deterioration of quality of life mainly due to the manifested pain and fatigue [1]. Adib et al. concluded that the delay in diagnosis of BJHS results in poor control of pain and fatigue and disruption of normal home life, schooling and physical activities. Knowledge of the diagnosis and simple interventions are likely to be highly effective in reducing the morbidity and cost to the health and social services [2].

Fatigue in BJHS appears as the result of multiple factors, including muscle weakness, respiratory insufficiency, unrefreshing sleep, dysautonomia, intestinal malabsorption, reactive depression/anxiety, and excessive use of analgesics [1].

Fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion [3]. Musculoskeletal disorders, including BJHS, are in general characterized by pain and fatigue with other physical disorders, leading to decreased quality of life and economic burdens to society [4]. Reviewing the medical literature, few studies focusing on fatigue and quality of life in BJHS were available. However, Murray and Woo investigated the burden of fatigue in children with BJHS in 2001 and reported that BJHS is a major source of morbidity in children and due to fatigue; activities of daily living, physical and sports activities may be limited [5].

One method of assessing the impact of a chronic illness on the daily life of children is to measure the health related quality of life. A comprehensive and multidimensional construct is the Pediatric Quality of Life inventory core scales (PedsQL); it addresses an individual's subjective perception of functioning across multiple domains, including physical, emotional, social, and school functioning [6]. The PedsQL generic core scales and multidimensional fatigue scale significantly distinguished between pediatric patients with fibromyalgia and healthy children [7].

Except for the recognized effectiveness of physiotherapy for some musculoskeletal features, there are no standardized guidelines for the assessment and treatment of pain and fatigue in BJHS [1]. However, management is more or less similar to other conditions characterized by fatigue. Multidisciplinary treatment combining graded exercise therapy, cognitive behavioral therapy and pharmacological treatment has shown short-term improvements [8].

Fatigue proved to be an important, but still neglected factor in BJHS treatment; the current study stressed on this symptom in order to further strengthen the awareness that fatigue is a serious aspect of the disease with far reaching consequences on the person's daily life. Because it turned out that fatigue – besides pain – is one of the most annoying symptom to handle in patients with rheumatic diseases [9];new knowledge about the relationship between fatigue and psychological and physical functioning might help to inform about new strategies and to improve existing treatments to combat fatigue.

The aim of the present study was to investigate the relationship between fatigue and health related quality of life in adolescents with BJHS.

2. Patients and methods

A cross sectional design was employed in the current study, which was carried out by performing a single clinical evaluation using the same standardized protocol to all the study subjects.

The study was conducted in the period between January 2012 and June 2012 in the Ain Shams University and Suez Canal University hospitals. The study population included 30 adolescent patients (12–18 years) with BJHS as diagnosed by applying the Brighton criteria (after calculating the Beighton score), in addition to 30 healthy control who were age and sex matched to the studied patients. An adolescent was defined as normal after clinical examination and based on declaration by parents. The patients and control groups were recruited from the pediatrics and the rheumatology clinics.

2.1. Clinical assessment

The Beighton score consists of 5 maneuvers (total score = 9):

- Opposition of the thumb to the volar aspect of the ipsilateral forearm (1 point for left; 1 for right).
- Passive dorsiflexion of the fifth metacarpal joint to $\geqslant 90°$ (1 point for left; 1 point for right).
- Hyperextension of the elbow to $\geqslant 10°$ (1 point for left; 1 point for right).
- Placing of hands flat on the floor without bending knees (1 point).
- Hyperextension of the knee to $\geqslant 10°$ (1 point for left; 1 point for right).

The Brighton criteria include:
Major Criteria

- A Beighton score of 4/9 or greater.
- Arthralgia for longer than 3 months in more than 4 joints.

Minor Criteria

- A Beighton score of 1, 2 or 3/9.
- Arthralgia > 3 months in 1-3 joints or back pain > 3 -months, spondylosis/spondylolisthesis.
- Dislocation/subluxation in > 1 joint, or 1 joint more than once.
- Soft tissue rheumatism (eg: epicondylitis, tenosynovitis, bursitis) > 3 lesions.

- Marfanoid habitus (tall, slim, span/height ratio > 1.03, upper/lower segment ratio less than 0.89, arachnodactyly, positive Steinberg/wrist signs).
- Abnormal skin: striae, hyper-extensible skin.
- Eye signs: drooping eyelids or myopia or antimongoloid slant.
- Varicose veins or hernia or uterine/rectal prolapse.

Diagnosis of BJHS is confirmed in the presence of two major criteria, or one major and two minor criteria, or four minor criteria [10].

All adolescents underwent clinical assessment in the form of general medical history taking and examination with stress on the musculoskeletal system. Exclusions included acute illness such as common cold and gastroenteritis, chronic diseases (diabetes, renal impairment, malignancy etc) and other rheumatic diseases including fibromyalgia and chronic fatigue syndrome (CFS). Following laboratory assessment, any patient who showed any abnormal result was also excluded.

A written consent was obtained from parents of all participants. All patients and control groups completed a self assessment pediatric quality of life [11], and multidimensional fatigue scale [12] questionnaires which were translated into Arabic language. Regarding the validity of the translation process, the authors and other expert concluded that it is face valid. For test- retest reliability, the questionnaires were tested on a group of normal children ($n = 20$) and then repeated (r coefficient was 0.8).The study was approved by the local ethics committee and complies with the Helsinki declaration.

2.2. Measures

Health-related quality of life was assessed using the Pediatric Quality of Life inventory (PedsQL) generic core scales, version 4.0 [11], while for fatigue, the multidimensional fatigue scale [12] was employed. The PedsQL generic core scales version 4.0 consists of 23 items which can be completed independently by adolescents. It includes four domains that measure physical functioning, emotional functioning, social functioning and school functioning. The instructions ask how much of a problem each item has been during the past one month. A 5-point response scale is utilized (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem).Items are reverse-scored and linearly transformed into a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQoL. Scale Scores are computed as the sum of the items divided by the number of items answered. The minimum total score is 0 and the maximum is 100 for each domain. The multidimensional fatigue scale includes 3 domains; general fatigue, sleep/ rest fatigue and cognitive fatigue. It consists of 18 items. The format, instructions, scale and scoring method are identical to the PedsQL 4.0 generic core scales, with higher scores indicating better HRQoL (fewer problems or symptoms) .The minimum total score is 0 and the maximum is 100 for each domain.

General fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion [3]. Cognitive fatigue was defined as a failure to sustain attention that requires self-motivation to optimize performance [13].Sleep / rest fatigue as defined from the multidimensional fatigue scale includes any of increased period of sleep, finding it hard to sleep through night, taking a lot of naps and spending a lot of time in bed.

Adolescents independently completed their questionnaires. Assistance by the physician was provided if required.

2.3. Visual analogue scale (VAS) pain intensity assessment

The VAS intensity rating consisted of a 100 mm horizontal line with the end points no pain and worst pain. The far left end indicates 'No pain' and the far right end indicates 'Worst pain ever'. Study participants were asked to make a mark on the line that represented their current pain intensity, and the VAS pain intensity level was scored by measurement in millimeters of the distance from the no pain end of the line to the point marked by the patient.

2.4. Laboratory assessment

Laboratory assessment for adolescents with BJHS included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), anti nuclear antibody (ANA), IgM rheumatoid factor, anticitrulline peptide antibody (ACPA), serum calcium, alanine aminotransferase (ALT),aspartate aminotransferase (AST), serum creatinine and thyroid stimulating hormone (TSH).

Statistical analysis: The data were collected and processed to a personal computer IBM compatible. Data were analyzed with the aid of the program statistical package for social science (SPSS) 10 for windows. The data were tested for normality by using Shapiro-Wilk test ($P > 0.05$) for all variables. So, parametric tests (t-test and regression analyses) were used for the continuous variables. Pearson Chi square test was used to compare categorical variables.

Multiple linear regression analyses were conducted between the total PedsQL score and its domains as dependent variables and a list of independent variables to identify the predictors of the quality of life. The independent variables included patients' age, gender, body mass index (BMI), type of the study group, VAS score, multidimensional fatigue scale total and domains, hemoglobin level, ESR, serum calcium, TSH, creatinine, ALT, and AST.

3. Results

The study enrolled 30 adolescents with BJHS (17 males and 13 females) and 30 normal adolescents (15 males and 15 females) .Both groups were gender matched ($X^2 = 0.268$, $p = 0.605$) and age matched (Table 1).

We excluded 2 patients suspected to have fibromyalgia; the specific tender points for the syndrome were detected on examination .Following laboratory assessment 7 patients were excluded; 3 for high ESR, 2 for high CRP and 2 for severe iron deficiency anemia.

The disease duration ranged from 3 to 13 months (mean ± SD = 7.87 ± 2.24). Regarding the principal complaint of the patients, 17/30 [9 males (30%) and 8 females (26.67%)] presented with the complaint of fatigue, 7/30(23.34%) with arthralgia (knees in 6 and ankles in 1), 4/30 (13.34%) with low back pain and 2/30 (6, 67%) with feet pain. None of the studied patients had symptoms (other than fati-

Table 1 Comparison between BJHS and control groups regarding demographic and laboratory data.

	Patients $n = 30$ mean ± SD	Control $n = 30$	t	p
Age (years)	13.8 ± 1.9	14 ± 0.8	0.51	0.68
BMI (Kg/m^2)	23.83 ± 4.11	24 ± 4.06	−0.16	0.88
TLC (×10^3/mm^3)	7.01 ± 1.66	7.1 ± 1.81	−0.19	0.85
RBC count (×10^6/mm^3)	4.84 ± 0.39	4.84 ± 0.43	−0.03	0.98
Platelet count (×10^3/mm^3)	336.7 ± 54.24	323.6 ± 52.89	0.95	0.35
Hemoglobin (×10^3/mm^3)	13.84 ± 1.17	14.17 ± 1.26	−1.06	0.29
ESR (mm/h)	14.17 ± 3.97	13.7 ± 3.04	0.51	0.61
ALT (IU/L)	20.93 ± 5.64	18.53 ± 7.78	1.37	0.18
AST (IU/L)	18.77 ± 4.62	18.53 ± 7.22	0.15	0.88
Creatinine (mg/dL)	0.68 ± 0.17	0.63 ± 0.18	1.03	0.31
TSH (μIU/L)	2.96 ± 0.62	3.13 ± 0.76	−0.95	0.35
Calcium (mg/dL)	9.47 ± 0.54	9.54 ± 0.57	−0.54	0.59

BJHS: benign joint hypermobility syndrome; TLC: total leukocyte count; RBCs: red blood cells; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TSH: thyroid stimulating hormone; SD: standard deviation.

gue) suggestive of autonomic nervous system affection. None of the patients had history consistent with joint dislocation or joint subluxation. History of a previous attack of ankle sprain was found in 5/30 patients, otherwise none of the patients gave history consistent with arthritis, and on musculoskeletal examination none showed signs of arthritis. None of the included patients had any associated or underlying connective tissue disease dysplasia. None of the patients was regularly using analgesics, and at the time of inclusion in the study, none of the patients was on analgesics for symptom relief. Patients were requested to stop it (if any) for two weeks prior to inclusion in the study. None of the included healthy controls complained of fatigue or any other musculoskeletal manifestations. Fig. 1 illustrates 4/5 maneuvers of the Beighton score as obtained from our BJHS patients.

CRP, ANA, IgM rheumatoid factor, and ACPA were negative in all enrolled subjects. Results of the other laboratory investigations are illustrated in Table 1.

All items of the PedsQL and the multidimensional fatigue assessment questionnaires were completed by patients and controls. The mean values of the 4 domains of the PedsQL questionnaire, the 3 domains of the multidimensional fatigue scale and VAS score in patients compared to controls are illustrated in Table 2. Adolescents with BJHS recorded considerably lower scores for all the 7 items of both scales ($p < 0.001$). Their lowest scores were in the school function and the general fatigue domains. VAS score was significantly higher in patients' group.

The strength of the univariate relationships between the total PedsQL scores and the predictor variables are shown in Table 3. General fatigue domain, cognitive fatigue domain and type of the study group were the significant independent predictors of the total PedsQL score. Also, the total score of the multidimensional fatigue scale was a significant independent predictor of the PedsQL total score ($t = 4.828$, $p < 0.001$). There was a negative linear association between type of the study group and the PedsQL total score. In other words, the scores were significantly higher in the control group than the patients' group.

The total multidimensional fatigue scale score was a significant predictor for the physical function domain score ($t = 7.812$, $p < 0.001$). On further multiple linear regression analysis for other predictors of the physical function domain, general fatigue and cognitive fatigue scores were also found to be significant predictors (Table 4). There was no association between the type of the study group and physical domain score i.e. there was no significant difference between patients and controls. Table 4 shows that the significant independent predictors of school function domain were type of the study group and the cognitive fatigue score. There was a negative linear association between the study group and the emotional, social and school function domain scores i.e. the scores were significantly higher in the control group than the patients' group.

The only significant predictors of emotional function domain were the type of the study group ($t = 7.22$, $p < 0.001$) and the general fatigue score ($t = 3.05$ $p = 0.004$), while the only significant independent predictors of social function domain were type of the study group ($t = -11.95$, $p < 0.001$) and the general fatigue score ($t = 3.27$ $p = 0.002$).Data are illustrated in Table 5.

There was a significant correlation between VAS and the PedsQL and the multidimensional fatigue scales and their domains in the BJHS group (Table 6). However, in the regression models (Tables 4 and 5) VAS was not a predictor of PedsQL and its domains; the significantly high bivariate correlations between the dependent variables (BJHS, VAS and fatigue) are the cause of amelioration of the effect of VAS when included in the regression models.

4. Discussion

In discussion the present study revealed that health related quality of life is diminished in adolescents with BJHS compared with age and gender-matched controls. Patients with BJHS reported an impact of disease on emotional, social and school function domains of the PedsQL. Fatigue which accompanies BJHS is a significant predictor of the reduced health related quality of life in those patients. Pain was highly correlated to fatigue and health related quality of life.

Dysautonomia is one of the extra-articular manifestations in joint hypermobility syndrome. Symptoms related to the autonomic nervous system, such as syncope and presyncope, palpitations, chest discomfort, fatigue, and heat intolerance, are more common among patients compared to controls [14]. In our series fatigue was the only assessed of these symptoms, and none of the patients gave history suggestive of other dys-

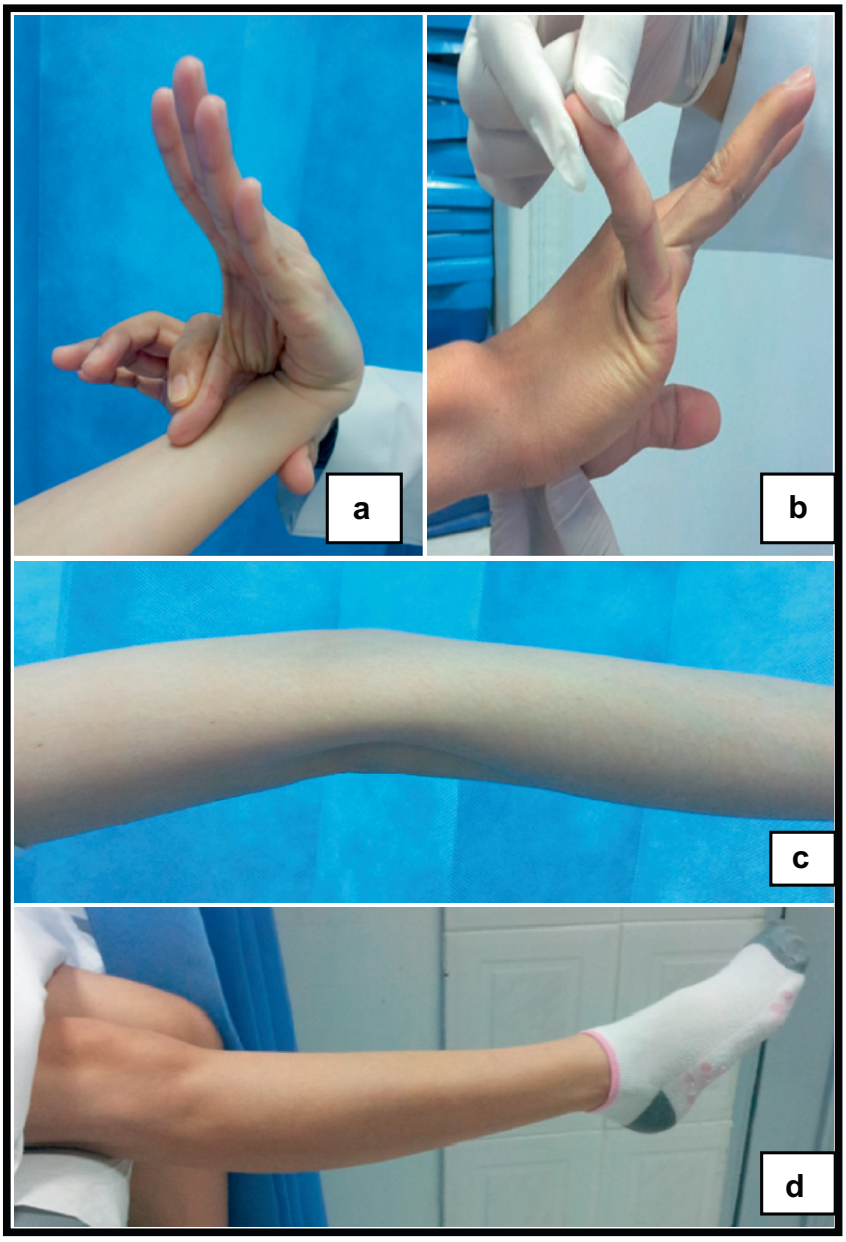

Figure 1 Maneuvers of the Beighton score. (a) opposition of the thumb to the volar aspect of the ipsilateral forearm, (b) passive dorsiflexion of the fifth metacarpal joint to $>90°$, (c) hyperextension of the elbow joint to $>10°$ and (d) hyperextension of the knee joint to $>10°$.

autonomia manifestations. However, investigating other autonomic nervous system manifestations was beyond the scope of our aim.

In the current study, fatigue along with BJHS was the only significant predictors of the diminished health related quality of life in the patients' group. This association was proved for other chronic illnesses affecting the pediatric population. Among survivors of childhood cancer, an inverse relationship exists between symptoms of fatigue and a patient's positive perception of health related quality of life. Notably, survivors who did not report fatigue were comparable to healthy controls on measures of functioning [15]. In children with primarily inactive inflammatory bowel disease (IBD), fatigue was significantly higher and health related quality of life was significantly lower than in healthy controls. Results among children with IBD were comparable to children with rheumatologic diseases and cancer [16].

On history taking and clinical examination patients suspected to have any other cause of fatigue were excluded. In addition, patients with abnormal laboratory results were excluded, and no difference was recorded between the enrolled patients and controls regarding all laboratory results. So, it is likely that the recorded fatigue in our series was related to BJHS and not to other diseases. Furthermore, multiple regression analysis revealed that age, gender, BMI and laboratory results were not predictors of any of the PedsQL domains while

Table 2 Comparison between BJHS and control groups regarding scores of the domains of PedsQL and multidimensional fatigue scales and VAS score.

	Patients' group $n = 30$ mean ± SD	Control group $n = 30$	t	p
PedsQL				
Physical	54.58 ± 18.02	81.77 ± 9.18	−7.37	<0.001
Emotional	56.17 ± 11.27	89.67 ± 3.46	−15.56	<0.001
Social	55.67 ± 7.16	89.33 ± 5.04	−21.06	<0.001
School	43.83 ± 20.71	89.83 ± 5.80	−11.72	<0.001
Total	52.56 ± 8.40	87.63 ± 4.68	−19.98	<0.001
Multidimensional fatigue scale				
General	63.75 ± 19.08	88.47 ± 5.65	−6.80	<0.001
Sleep/rest	73.89 ± 17.44	92.77 ± 5.13	−5.69	<0.001
Cognitive	66.95 ± 15.12	92.64 ± 4.05	−8.99	<0.001
Total	66.09 ± 13.05	91.32 ± 3.97	−10.14	<0.001
VAS score	33.90 ± 13.04	8.57 ± 4.06	10.16	<0.001

BJHS: benign joint hypermobility syndrome; VAS: visual analogue scale.*p value is statistically significant at <0.05.

Table 3 Multiple regression analysis: predictors of the total PedsQL score in BJHS group.

	Standardized Beta coefficients	t	p
Constant		2.05	0.05
Age	0.04	1.00	0.32
Gender	0.03	0.85	0.40
BMI	0.01	0.27	0.79
BJHS	−0.61	−9.08	0.00
General fatigue	0.34	4.29	0.00
Sleep/rest fatigue	−0.02	−0.20	0.84
Cognitive fatigue	0.12	2.07	0.04
VAS score	−0.49	−.38	0.71
ESR	−0.06	−1.54	0.13
Hemoglobin level	0.03	0.74	0.46
Serum calcium	−0.02	−0.46	0.65
TSH	0.03	0.72	0.48
ALT	0.05	0.85	0.40
AST	0.00	0.09	0.93
Creatinine	0.01	−0.23	0.82

Dependent variable: PedsQL total score. BJHS: benign joint hypermobility syndrome; BMI: body mass index; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; TSH: thyroid stimulating hormone; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

fatigue was a significant predictor .This could imply that fatigue is the cause of the impaired health related quality of life recorded in our series.

Fatigue is a critical contributor to the impact of chronic illness on multiple domains of functioning. In juvenile rheumatoid arthritis (JRA) maintenance of a social life is negatively influenced by physical fatigue, reduced activity, pain and depressive symptoms [17]. Furthermore, in those patients fatigue reduces the patients' self-esteem; heightens irritability, and feelings of loss of control [9].In the current study, BJHS was the significant predictor for emotional, social and school function impairment. In addition, general fatigue was a predictor for emotional and social function impairment; while cognitive fatigue was the predictor for school function impairment. This denotes that fatigue which associates BJHS is a direct cause of impairment of multiple domains of function. In chronic diseases characterized by relapse and remission, fatigue is even manifested in the remission periods. In patients with IBD, in remission, fatigue is an important feature. Both in Crohn's disease and in ulcerative colitis, fatigue determined health related quality of life independent of disease activity or anemia [18]. Subsequent studies also proved that fatigue is associated with reduction of health related quality of life scores in IBD, where the physical domains are particularly affected [19]. This could imply that in patients with BJHS, fatigue could be the major or even the only complaint. This was the case in 17 out of our 30 patients.

Delay in diagnosis of BJHS results in poor control of pain and fatigue and disruption of normal home life, schooling and physical activities [2]. Once symptoms of cognitive or neuropsychiatric nature are established, cognitive, behavioral, emotional, physiological and social factors are thought to work together to perpetuate those symptoms [20]. In our patients, school function was the most affected domain. Cognitive fatigue which associates BJHS was a significant predictor of school function impairment. Accordingly, early recognition of cognitive fatigue symptoms could be beneficial in preventing deterioration at the school level through cognitive rehabilitation procedures. In chronic fatigue syndrome (CFS), evidence of clear cognitive impairment independent of psychopathology deficits remain even when factors associated with performance impairments are taken into consideration. Improvements or recovery from the illness was postulated to be accompanied by improvements in cognition [21].

Fatigue, mainly general and cognitive, was a predictor for the impaired physical function in patients and controls. The recorded fatigue in controls; though is of lower magnitude, in not surprising. Approximately one third of normal healthy adolescents experience substantial fatigue four or more times a week [22]. However, the present study recorded a statistically significant difference between BJHS patients and controls in PedsQL and fatigue scores. This alleviates the possibility that fatigue in adolescents with BJHS is of the same frequency and severity found in normal adolescents.

More than three-quarters of Ehlers–Danlos Syndrome (EDS) patients suffer from severe fatigue and the possible determinants of fatigue are sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain severity [23]. Of special interest is the Ehlers–Danlos Syndrome hypermobility type (EDS-HT) which is closely

Table 4 Multiple regression analysis: predictors of the physical function and school function domains in BJHS group.

	Physical function domain score			School function domain score		
	Standardized Beta coefficients	*t*	*p*	Standardized Beta coefficients	*t*	*p*
Constant		−1.42	0.16		0.50	0.62
Age	0.09	1.72	0.09	0.06	0.69	0.49
Gender	−0.04	−0.72	0.48	0.09	1.08	0.29
BMI	0.06	1.14	0.26	−004	−0.45	0.65
BJHS	−0.01	−0.14	0.89	−0.60	−4.17	0.00
General fatigue	0.63	6.13	0.00	005	0.31	0.76
Cognitive fatigue	0.20	2.57	0.01	0.33	2.61	0.01
Sleep/Rest fatigue	0.19	1.92	0.06	−0.12	−0.71	0.48
VAS score	2.12	1.26	0.22	−1.34	−0.49	0.63
ESR	−0.10	−1.86	0.07	−0.07	−0.84	0.40
Hemoglobin level	−0.05	−0.88	0.38	0.10	1.07	0.29
Serum calcium	−0.03	−0.52	0.61	−0.04	−0.49	0.63
TSH	0.01	0.23	0.82	0.07	0.81	0.42
ALT	0.15	1.71	0.09	−0.01	−0.09	0.93
AST	0.02	0.30	0.77	0.01	0.13	0.90
Creatinine	−0.00	−0.05	0.96	−0.02	−0.22	0.83

Dependent variable: PedsQL physical function and school function domain scores. BJHS: benign joint hypermobility syndrome; BMI: body mass index; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; TSH: thyroid stimulating hormone; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 5 Multiple regression analysis: predictors of the emotional function and social function domains in BJHS group.

	Emotional function domain score			Social function domain score		
	Standardized Beta coefficients	*t*	*p*	Standardized Beta coefficients	*t*	*p*
Constant		3.37	0.002		3.34	0.002
Age	−0.06	−1.08	0.29	0.05	1.16	0.25
Gender	0.04	0.66	0.52	−0.00	−0.06	0.95
BMI	−0.02	−0.37	0.71	0.06	1.52	0.14
BJHS	−0.75	−7.22	0.000	−0.86	−11.95	0.000
General fatigue	0.37	3.05	0.004	0.28	3.27	0.002
Cognitive fatigue	0	−0.98	0.33	−0.11	−1.73	0.09
Sleep/Rest fatigue	−0.06	−0.50	0.62	−0.11	−1.73	0.09
VAS score	−2.17	−1.10	0.28	−0.06	−0.04	0.97
ESR	−0.02	−0.32	0.75	−0.02	−0.48	0.64
Hemoglobin level	0.01	0.19	0.85	0.03	0.54	0.59
Serum calcium	−0.03	−0.42	0.67	0.04	0.96	0.34
TSH	0.00	0.06	0.96	0.00	0.05	0.96
ALT	−0.02	−0.19	0.85	0.07	0.99	0.33
AST	−0.00	0-.05	0.96	−0.02	−0.36	0.72
Creatinine	−0.02	−0.27	0.79	−0.03	−0.65	0.52

Dependent variable: PedsQL emotional function and social function domain scores. BJHS: benign joint hypermobility syndrome; BMI: body mass index; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; TSH: thyroid stimulating hormone; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

related, clinically, to BJHS [24]. Those patients manifest significant joint pain, joint dislocations, muscle cramps, tendinitis, fatigue and headache, and their health related quality of life was reported as significantly impaired [25]. The significant fatigue and impairment of quality of life elicited in our BJHS group could provide some support to the notion that both syndromes (EDS-HT and BJHS) share many of the clinical manifestations; taking into consideration that we did not study the factors reported to determine fatigue in EDS.

Joint hypermobility is more common in patients with CFS than in otherwise healthy children with common skin disorders; significantly more incident and prevalent CFS cases had Beighton scores of $\geqslant 4$ [26].The detected hypermobility in CFS patients could be related to coexisting EDS [27], although other studies argued such hypothesized association [28]. In our study, patients suspected to have CFS were excluded and the direct cause of the significant fatigue and quality of life impairment is BJHS.

Fatigue is prevalent among children with different rheumatic diseases and fatigue is strongly associated with increased pain and decreased quality of life [29]. Preacher and Hayes [30] proposed a mediation model for fatigue. They proposed that fatigue functioned as a mediator between pain and overall health related quality of life based on both self and proxy reports. Later, a similar mediation model was also proposed where fatigue was hypothesized to mediate the effects of pain on children's health related quality of life, specifically their

Table 6 The correlation between visual analogue scale and PedsQL and multidimensional fatigue scales in BJHS group.

	VAS score	
	r	*p*
BJHS	0.80*	< 0.001
PedsQL total score	−0.88*	< 0.001
Physical function domain	−0.88*	< 0.001
School function domain	−0.72*	< 0.001
Social function domain	−0.81*	< 0.001
Emotional function domain	−0.78*	< 0.001
Multidimensional fatigue scale total score	−0.99*	< 0.001
General fatigue	−0.862*	< 0.001
Cognitive fatigue	−0.75*	< 0.001
Sleep/Rest fatigue	−0.84*	< 0.001

VAS: visual analogue scale; BJHS: benign joint hypermobility syndrome.
* Correlation is significant at < 0.01 level (2-tailed).

school functioning [31].In the present study, pain was more significant in BJHS group and was highly correlated to fatigue and PedsQL. This result could support the postulated meditational role of fatigue in the relationship between pain and the overall health related quality of life.

Limitations of the study include the relatively small number of the study population, so our results are considered preliminary. In addition, the study was limited to a definite age group and it is not known if results could be applied to patients with BJHS of all age groups. The cross sectional design does not permit follow up of patients to evaluate for possible variation of symptoms following different suggested interventions, also the cross-sectional nature of the study does not permit for any firm conclusion regarding the direction of causal relationships to be made. Studies incorporating simultaneous assessment of the other different factors, implicated as causes of fatigue in BJHS, are expected to highlight the most important ones for subsequent possible interventions.

The conclusion gained from the current study is that adolescents with BJHS compared to controls have significant fatigue that leads to reduced health related quality of life. Their emotional, social and school function is disturbed because of the manifested fatigue. Although physical function reduction associated with total, general and cognitive fatigue occurred both in patients and controls; impairment was greater in the patients' group. Pain was more significant in BJHS group and was correlated to both health related quality of life and fatigue. Owing to the small number of patients enrolled, the results of the present study are preliminary; the high prevalence of fatigue in BJHS emphasizes the need for further detailed prospective research to better understanding of its etiology, course and management.

Conflict of interest

All the authors responsible for this work declare no conflict of interest.

References

[1] Castori M, Morlino S, Celletti C, Celli M, Morrone A, Colombi M, et al. Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers–Danlos syndrome, hypermobility type): principles and proposal for a multidisciplinary approach. Am J Med Genet A 2012;158A(8):2055–70.
[2] Adib N, Davies K, Grahame R, Woo P, Murray KJ. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology 2005;44:744–50.
[3] Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996;9:456–60.
[4] Engelbert RH, Kooijmans FT, van Riet AM, Feitsma TM, Uiterwaal CS, Helders PJ. The relationship between generalized joint hypermobility and motor development. Pediatr Phys Ther 2005;17(4):258–63.
[5] Murray K, Woo P. Benign joint hypermobility in children. Rheumatology 2001;40(5):489–91.
[6] Gold JI, Mahrer NE, Yee J, Palermo TM. Pain, fatigue and health-related quality of life in children and adolescents with chronic pain. Clin J Pain 2009;25(5):407–12.
[7] Varni JW, Seid M, Smith Knight T, Burwinkle T, Brown J, Szer IS. The PedsQL in pediatric rheumatology: reliability, validity, and responsiveness of the pediatric quality of life inventory generic core scales and rheumatology module. Arthritis Rheum 2002;46(3):714–25.
[8] Núñez M, Fernández-Solà J, Nuñez E, Fernández-Huerta JM, Godás-Sieso T, Gomez-Gil E. Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioral therapy and graded exercise versus usual treatment. A randomized controlled trial with 1 year of follow-up. Clin Rheumatol 2011;30(3):381–9.
[9] Hewlett S, Cockshott Z, Byron M, Kitchen K, Tipler S, Pope D, et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Rheum 2005;15(53):697–702.
[10] Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 2000;27:1777–9.
[11] Varni JW, Seid M, Kurtin PS. Peds QL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–12.
[12] Varni JW, Burwinkle TM, Szer IS. The PedsQL multidimensional fatigue scale in pediatric rheumatology: reliability and validity. J Rheumatol 2004;31(12):2494–500.
[13] Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004;363(9413):978–88.
[14] Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med 2003;115(1):33–40.
[15] Meeske KA, Patel SK, Palmer SN, Nelson MB, Parow AM. Factors associated with health-related quality of life in pediatric cancer survivors. Pediatr Blood Cancer 2007;49:298–305.
[16] Marcus SB, Strople JA, Neighbors K, Weissberg-Benchell J, Nelson SP, Limbers C, et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. Clin Gastroenterol Hepatol 2009;7:554–61.
[17] Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, Van de Bos GAM. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis & Rheumatism 2004;51:578–85.
[18] Romberg-Camps MJ, Bol Y, Dagnelie PC, Hesselink-van de Kruijs MA, Kester AD, Engels LG, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg cohort. Inflamm Bowel Dis 2010;16:2137–47.
[19] Jelsness-Jørgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. Aliment Pharmacol Ther 2011;33:106–14.
[20] Surawy C, Hackman A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behav Res Ther 1995;33:535–44.

[21] Thomas M, Smith A. An investigation into the cognitive deficits associated with chronic fatigue syndrome. Open Neurol J 2009;3:13–23.
[22] Viner R, Christie D. Fatigue and somatic symptoms. BMJ 2005;330:1012–5.
[23] Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. Fatigue is a frequent and clinically relevant problem in Ehlers–Danlos Syndrome. Semin Arthritis Rheum 2010;40(3):267–74.
[24] Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. The lack of clinical distinction between the hypermobility type of Ehlers–Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet A 2009;149A(11):2368–70.
[25] Rombaut L, Malfait F, Cools A, De Paepe A, Calders P. Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers–Danlos syndrome hypermobility type. Disabil Rehabil 2010;32(16):1339–45.
[26] Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr 2002;141(3):421–5.
[27] Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers–Danlos syndrome. J Pediatr 1999;135(4):494–9.
[28] van de Putte EM, Uiterwaal CS, Bots ML, Kuis W, Kimpen JL, Engelbert RH. Is chronic fatigue syndrome a connective tissue disorder?. A cross-sectional study in adolescents. Pediatrics 2005;115(4):415–22.
[29] Aviel YB, Stremler R, Benseler SM, Cameron B, Laxer RM, Ota S, et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. Rheumatology 2011;50(11): 2051–60.
[30] Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004;36:717–31.
[31] Berrin SJ, Malcame VL, Varni JW, Burwinkle TM, Sherman SA, Artavia K, et al. Pain, fatigue, and school functioning in children with cerebral palsy: a path-analytic model. J Pediatr Psychol 2007;32:330–7.